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Taastrup, 14 January 2003

Karin Schlichting
Head Clerk

PATENT- OG VAREMÆRKESTYRELSEN

FIELD OF INVENTION

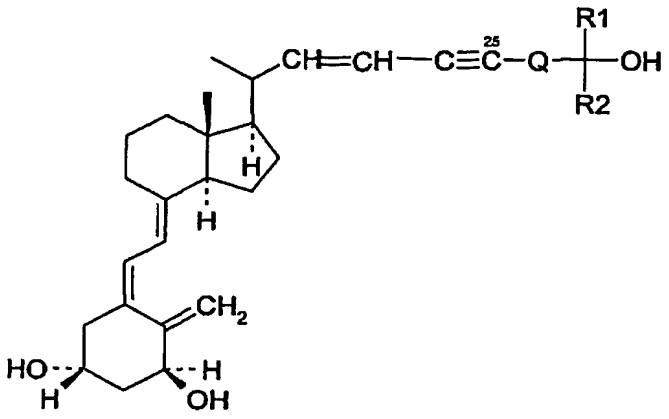
This invention relates to novel vitamin D analogues, to their use in therapy, to pharmaceutical compositions comprising said analogues, to methods of treatment comprising the administration of said analogues to patients in need thereof, and to the use of said analogues in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

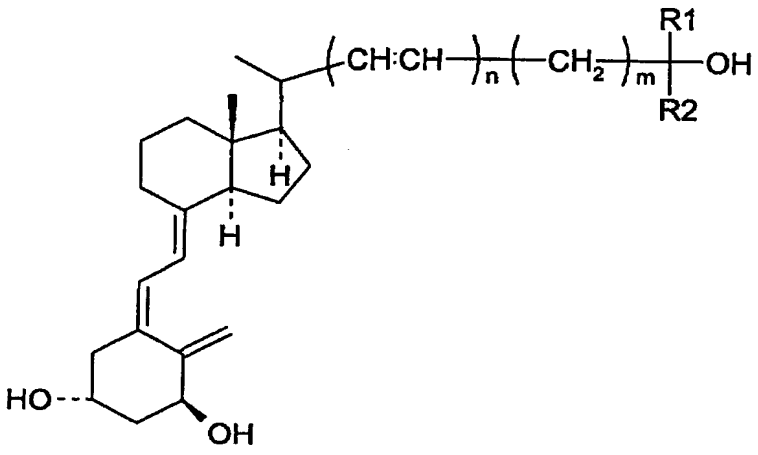
Over the last decades there has been a growing understanding of the biological effects of vitamin D. The classical actions of vitamin D involve calcium and phosphate absorption from the intestines, which is vital to the mineral balance and to the build-up and maintenance of bones. Another primary action of vitamin D is the regulation of the excretion of the parathyroid hormone from the parathyroid glands. Vitamin D inhibits the production of the parathyroid hormone, so that a low level of vitamin D in the blood will lead to a high level parathyroid hormone, and *vice versa*. Vitamin D exerts its effect through an intriguing mechanism whereby the production of the mRNA which is translated into the parathyroid hormone, or a proform thereof, is inhibited. The impact of vitamin D in biological systems, however, reaches beyond these effects. Vitamin D appears to have profound effects on muscles, the immune system, the reproductive system, and cell proliferation and differentiation. Cells holding the vitamin D receptor (VDR) have, in fact, been found in many parts of the body, including the intestines, kidneys, prostate, bone, bone marrow, parathyroid glands, skin, liver, muscle and lymphoid tissue. The widespread existence of VDR have made vitamin D and analogues thereof attractive compounds for the treatment of various diseases including cancer, skin and bone diseases and autoimmune diseases.

The invention relates to a novel class of vitamin D analogues that shows a potent suppressive effect on the secretion of parathyroid hormone, i.e. which can be used in the treatment of secondary hyperparathyroidism (s-HPT). A crucial structural element in active vitamin D is two hydroxyl groups in positions 1 and 25. In contrast to that, the compounds of the present invention are characterised by a blocking of the 25-position in the vitamin D structure, so that they do not have hydroxyl groups in that position, nor can they be hydroxylated in that position.

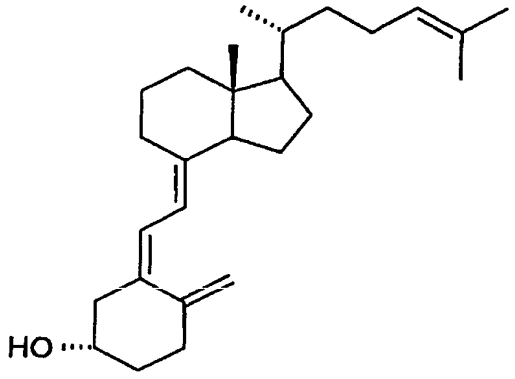
Vitamin D analogues with some structural resemblance to the compounds of the present invention have previously been disclosed. As an example, WO95/02577 teaches compounds of the formula



WO91/00855 discloses compounds of the formula



and Onisko, *Tetrahedron Lett.*, 1107-1108, 13, 1977 discloses a compound of the formula



which is useful for inhibition of liver enzymes responsible for hydroxylation of vitamin D_3 to 25-OH vitamin D_3.

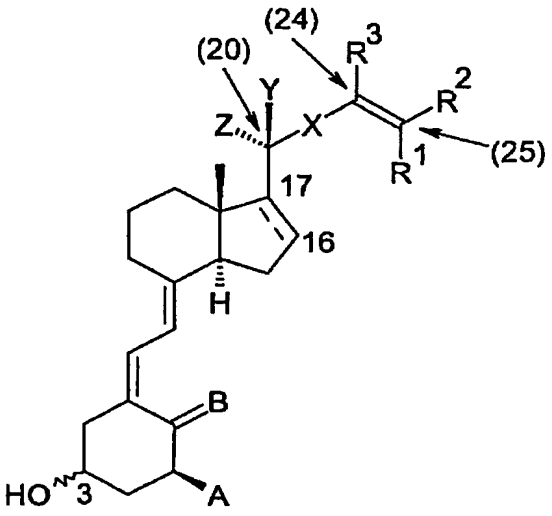
Finally, Bogoslovsky et al, *Vitamin D - Basic Research and its Clinical Application, proceedings of the Fourth Workshop on Vitamin D, Berlin West Germany 1979*, A. W. Norman et al (Eds.), p1257-1259, Walter de Gruyter, Berlin 1979, discloses a synthetic study including the preparation of 3(S)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene. This reference, however, does not disclose any biological data on this particular compound.

Vitamin D and analogues thereof are already used in the treatment of s-HPT. Paricalcitol (19-nor-1,25-dihydroxy-vitamin D_2) and doxercalciferol (1α-hydroxy-vitamin D_2) are approved in the USA for treatment of s-HPT, and 22-oxa-calcitriol (maxacalcitol) and hexafluoro-calcitriol (falecalcitriol) are approved in Japan [Malluche, *Kidney Int.*, 367-374, 62, 2002]. Moreover, calcitriol itself and and a prodrug thereof 1α(OH)D_3 are also used in the treatment and prophylaxis of s-HPT [Brandi, *Nephrol Dial Transplant*, 829-842, 17, 2002].

All therapeutic interventions which include administration of vitamin D and analogues thereof must pay attention to the adverse side effects often associated with this kind of therapy, in particular the calcemic effects of vitamin D compounds. These side effects may severely restrict or even prevent the use of such compounds, in spite of other clinically positive effects. The present invention therefore seeks to provide vitamin D analogues which have a reduced calcemic effect while retaining a suppressive effect on the secretion of the parathyroid hormone.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides compounds represented by formula I



I

in which formula

R1 and R2, which may be the same or different, represent hydrogen, halogen, (C_1-C_6)hydrocarbyl, optionally substituted with one or two hydroxyl group or one or more fluorine atoms, or, together with the carbon atom to which they are both attached, R1 and R2 form a (C_3-C_6)carbocyclic ring, or one of R1 and R2 taken together with R3 forms a direct bond, such that a triple bond is constituted;

R3 when not forming a direct bond with one of R1 and R2 represents hydrogen or (C_1-C_3)hydrocarbyl;

X represents ethynylene or, when R3 is hydrogen or hydrocarbyl, ethylene or ethynylene;

Y and Z independently represent hydrogen or methyl;

the bond between C#16 and C#17 is depicted with a dotted line to illustrate that said bond may be either a single bond, in which case the projection of the ring substituent is beta, or a double bond;

A represents hydroxyl, fluorine or hydrogen;

B represents CH_2 or H_2;

with the proviso that the compound of formula I is not 3(S)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene;

and prodrugs thereof.

In the compounds according to formula I, the blocking of the 25-position is achieved by the presence of a carbon-carbon double- or triple bond between carbon #24 and #25. In this

way, the 25-position cannot be hydroxylated. As discussed more thoroughly later, recent data suggest that hydroxylation in the 25-position has limited consequences for the parathyroid hormone suppressing effect. Vitamin D analogues which are blocked for hydroxylation in the 25-position therefore retain their parathyroid hormone suppressing effect while being deprived other vitamin D activities, e.g. the calcemic effect, associated with an intact vitamin D structure.

In another aspect, the invention relates to the use of a compound according to formula I in therapy.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound according to formula I.

In still another aspect, the invention relates to methods of treatment comprising the step of administering compounds according to formula I to a patient in need thereof.

In a still further aspect, the invention relates to the use of a compound according to formula I in the manufacture of a medicament.

DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment of the invention, R1 and R2 when taken separately represent hydrogen, methyl, trifluoromethyl, hydroxymethyl, (1- or 2-)hydroxyethyl, normal, iso- or cyclopropyl, 2-hydroxy-2-propyl, 2-methyl-2-propyl, 3-pentyl or 3-hydroxy-3-pentyl.

In another preferred embodiment, R1 and R2 when taken together include ethylene, tri-, tetra- and penta-methylene.

In another preferred embodiment, when R2 constitutes part of a triple bond, then R1 represents a branched C_{1-6} hydrocarbyl, optionally substituted with one or two hydroxyl groups. In particular, R1 represents a branched C_{1-6} hydrocarbyl, optionally substituted with one hydroxyl group, such as $-CMe_3$, $-C(OH)Me_2$ or $-C(OH)Et_2$.

In another preferred embodiment, R3, when not part of a triple bond, represents hydrogen, methyl or cyclopropyl.

In particular, compounds of formula I may be selected from amongst the list consisting of

1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 1),
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(Z),24-penta-ene (Compound 2),
20(S),1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 3),
1(S),3(R)-Dihydroxy-9,10-seco-26,27-cyclo-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 4),
20(S),1(S),3(R)-Dihydroxy-9,10-seco-26,27-cyclo-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 5),
1(S),3(R)-Dihydroxy-9,10-seco-26,27-methano-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 6),
20(S),1(S),3(R)-Dihydroxy-9,10-seco-26,27-methano-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 7),
1(S),3(R)-Dihydroxy-20(S)-(4,4-dibromo-1,3-butadien-1yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene (Compound 8),
1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 9),
20(S),1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 10),
1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(Z)-penta-ene (Compound 11),
20(S),1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(Z)-penta-ene (Compound 12),
1(S),3(R)-Dihydroxy-20(R)-(4-methyl-5-ethyl-5-hydroxy-1(E),3(E)-heptadienyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 13),
1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-1(E),3-butadienyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 14),
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),24-tetra-ene-22-yne (Compound 15),
1(S),3(R)-Dihydroxy-20(R)-(5-methyl-5-hydroxy-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 16),
1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1,3-heptadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 17),
1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1,3-heptadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 18),

1(S),3(R)-Dihydroxy-20(R)-(5,5-dimethyl-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 19),
1(S),3(R)-Dihydroxy-20(S)-(5,5-dimethyl-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 20),
1(S)-Fluoro-3(R)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 21),
1(S),3(R)-Dihydroxy-19-nor-9,10-secocholesta-5,7(E),22(E),24-tetra-ene (Compound 22),
1(S),3(S)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),22(E),24-penta-ene (Compound 23),
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),16,22(E),24-hexa-ene (Compound 24),
1(S),3(R)-Dihydroxxy-26,26,26,27,27,27-hexafluoro-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 25),
3(S),26-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 26).

Compounds of formula I may comprise chiral centres and carbon-carbon double bonds which give rise to the existence of stereo isomeric forms. The present invention relates to all such forms, either in pure form or as mixtures thereof.

The compounds of formula I may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or recrystallisation from an organic solvent or mixture of said solvent and a cosolvent that may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The invention covers all crystalline modifications and forms and also mixtures thereof.

In the present context, unless stated differently, the term "prodrug" is intended to indicate compounds in which one or more hydroxyl groups are masked as groups which can be reconverted to hydroxyl groups *in vivo* so as to provide compounds of formula I upon administration to a patient. Examples of said groups are esters, e.g carboxylic acid esters and phosphate acid esters. It is well-known that proforms of vitamin D are hydroxylated in the liver and kidneys to reach the biologically active state. In line with this, compounds of formula I in which A is hydroxyl are preferred ones, but compounds in which A is hydrogen are, in fact, another type of prodrug, which may be hydroxylated into an active state upon administration to a patient.

In the present context, the term "hydrocarbyl" is intended to indicate the radical obtained by removal of one hydrogen atom from a straight, branched, and/or cyclic, saturated or unsaturated hydrocarbon.

In the present context the term "halogen" is intended to indicate compounds from the seventh main group in the periodic table, i.e. fluoro, chloro, bromo and iodo, and in particular chloro and bromo.

The terms "normal" and "epi" when used to describe the absolute configuration of a compound of the present invention relates to the absolute configuration of the natural vitamin D_3 itself. Hence, if the configuration at a given carbon is referred to as "normal", it is the same configuration as vitamin D_3 has on that particular carbon atom. Likewise, if the configuration at a given carbon is referred to as "epi", it is the opposite configuration as vitamin D has on that particular carbon atom.

Of particular relevance for the present invention is the treatment of secondary hyperparathyrodism (s-HPT), e.g. in connection with renal failure, using vitamin D and its analogues. Hyperparathyrodism is a disease characterised by increased secretion of the parathyroid hormone from the parathyroid glands. In s-HPT, the cause for the elevated excretion is not malfunctioning of the glands, but rather factors outside the glands, e.g. failing kidneys. Vitamin D is absorbed from the food or produced in the skin in a proform which has to be activated to reach its biologically active state. Part of this activation takes place in the kidneys as a hydroxylation of the proform. In patients with failing kidneys, e.g. dialysis patients, this hydroxylation is impaired, resulting in a lower level of active vitamin D in the blood. As mentioned above, a low level of vitamin D leads to a high production of the parathyroid hormone, and this pathological condition is termed secondary hyperparathyroidism.

The parathyroid hormone has a powerful influence on the cells in the bones causing them to release calcium into the blood stream. Under non-pathological conditions this process is well-balanced to secure an adequate calcium level in the bones. However, at elevated parathyroid hormone levels for extended periods of time, the bones will lose too much calcium and will become brittle and thus more prone to fracture. This condition is referred to as osteodystrophy and osteomalacia from which renal patients are often suffering. Prolonged exposure to parathyroid hormones is also found to have toxic effects on many vital organs, e.g. the heart, skeletal muscles, the nerves and the reproductive system [Malluche, *Kidney Int.*, 367-374, 62, 2002].

One way of controlling the level of parathyroid hormone is to administer vitamin D or analogues thereof which will inhibit the secretion of said hormone. Such therapeutic intervention, however, may be hampered by serious adverse side effects often associated with vitamin D therapy. As mentioned previously, an effect of vitamin D and many analogues thereof is an increased uptake of calcium from the intestine which may lead to hypercalcemia. This effect may restrict the utility of vitamin D analogues, which in other respects are beneficial. The aim for much of the on-going vitamin D research is thus to minimize the calcemic effect while maximizing the clinical effect. Ideally, if the structural moieties in the vitamin D molecule responsible for the different activities of vitamin D were identified, it would be possible to manipulate these structures to obtain selectivity, e.g. no calcemic activity but high parathyroid hormone secretion suppressive effect. Unfortunately, no such clear structure-activity relation has been established yet. However, a recent observation by Brandi in *Nephrol Dial Transplant*, 829-842, 17, 2002 might be helpful in this respect. Brandi compares the PTH suppressive effect of calcitriol, i.e. $1,25(OH)_2$ D_3 and its proform, $1\alpha(OH)D_3$. $1\alpha(OH)D_3$ is hydroxylated in the liver to $1,25(OH)_2D_3$, and due to the different pharmacokinetics of the two compounds, the bioavailability of $1,25(OH)_2D_3$ was markedly lower when $1\alpha(OH)D_3$ was administered to the patient than when $1,25(OH)_2$ was administered. In spite of this difference in the availability of $1,25(OH)_2$ D_3 in the two dosing regimes, there was no significant difference in the suppression of the secretion of PTH. This leads to the speculation that the 25-hydroxyl group is not mandatory for the PTH suppressive effect. One way of achieving the desired selectivity could thus be to block the 25-position in the vitamin D structure so that it cannot be hydroxylated, and in this way maintaining or even increasing the PTH suppressive effect while dispossessing the molecule of other vitamin D related activities, and in particular its calcemic effect.

In a particular embodiment, the invention thus provides a method for treating, preventing or ameliorating s-HPT, and in particular s-HPT associated with renal failure, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I. Optionally, said method may include treatment with other therapeutically active compounds normally used in the treatment of the above mentioned disease. Said compounds may be administered concomitantly or sequentially with compounds of the present invention, and in they particular include phosphate binders.

The use of compounds of the present invention may not be limited to the treatment of s-HPT. It is well-known that vitamin D and analogues thereof may be beneficial in the treatment of a variety of diseases due to a strong activity in inducing differentiation and

inhibiting undesirable proliferation of certain cells, including skin cells and cancer cells, as well as an immunomodulating effect and an effect in bone build-up and maintenance. Accordingly, the invention also provides a method of treating, preventing or ameliorating diseases characterised by abnormal cell differentiation and/or cell proliferation, cancer, leukemia, mammary cancer, brain glial cancer, osteosarcoma, melanoma, myelofibrosis, psoriasis, primary hyperparathyroidism, diabetes melitus, discoid and systemic lupus erythematosus, chronic dermatoses of autoimmune type, hypertension, acne, alopecia, skin aging, AIDS, neurodegenerative disorders, Alzheimer's disease, host versus graft and graft versus host reactions, rejections of transplants, steroid induced skin atrophy and osteroporosis, and for inducing osteogenisis, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I. Optionally, said method may include treatment with other therapeutically active compounds normally used in the treatment of the above mentioned diseases. Said compounds may be administered concomitantly or sequentially with compounds of the present invention, and they include phosphate binders, steroids and anti-proliferative agents.

In the systemic treatment using the present invention daily doses of from 0.001-2 µg per kilogram body weight, preferably from 0.002-0.3 µg/kg of mammal body weight, for example 0.003-0.3 µg/kg of a compound of formula I is administered, typically corresponding to a daily dose for an adult human of from 0.1 to 200 µg. A suitable dosing regime may, however, also include dosing with longer intervals, e.g. every other day, every week, or even with longer intervals. In the topical treatment of dermatological disorders, ointments, creams or lotions containing from 0.1-1000 µg/g, and preferably from 0.1-500 µg/g, for example 0.1-200 µg/g of a compound of formula I is administered. For topical use in ophthalmology ointments, drops or gels containing from 0.1-1000 µg/g, and preferably from 0.1-500 µg/g, for example 0.1-100 µg/g of a compound of formula I is administered. The oral compositions are formulated, preferably as tablets, capsules, or drops, containing from 0.07-100 µg, preferably from 0.1-50 µg, of a compound of formula I per dosage unit.

In a further preferred aspect, the invention relates to a pharmaceutical composition comprising a compound of formula I. The formulations of the present invention, both for veterinary and for human medical use, comprise active ingredients in association with a pharmaceutically acceptable carrier(s) and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

Conveniently, dosage unit of a formulation contain between 0.05 µg and 100 µg, preferably between 0.1 µg and 50 µg of a compound of formula I.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The formulations include e.g. those in a form suitable for oral (including sustained or timed release), rectal, parenteral (including subcutaneous, intraperitoneal, intramuscular, intraarticular and intravenous), transdermal, ophthalmic, topical, nasal or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy, e.g as disclosed in Remington, The Science and Practice of Pharmacy, 20th ed., 2000. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid, such as ethanol or glycerol; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Such oils may be edible oils, such as e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carbomers and polyvinylpyrrolidone. The active ingredients may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form such as a powder or

granules, optionally mixed by a binder, such as e.g. lactose, glucose, starch, gelatine, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyethylene glycol, waxes or the like; a lubricant such as e.g. sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as e.g. starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the like or a dispersing agent, such as polysorbate 80. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be may in the form of suppositories in which the compound of the present invention is admixed with low melting water soluble or insoluble solids such as cocoa butter, hydrogenated vegetable oils, polyethylene glycol or fatty acids esters of polyethylene glycols, while elixirs may be prepared using myristyl palmitate.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. The formulation may be conveniently sterilised by for instance filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in *e.g.* Encyclopedia of Pharmaceutical Tehcnology, vol.9, 1994, are also suitable for parenteral administration.

Alternatively, the compound of formula I may be presented as a sterile, solid preparation, *e.g.* a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

Transdermal formulations may be in the form of a plaster or a patch.

Formulations suitable ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients, which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems e.g. as disclosed in Encyclopedia of Pharmaceutical Tehcnology, vol.2, 1989, may also be used to present the active ingredient for ophthalmic administration.

Formulations suitable for topical or ophthalmic administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers.

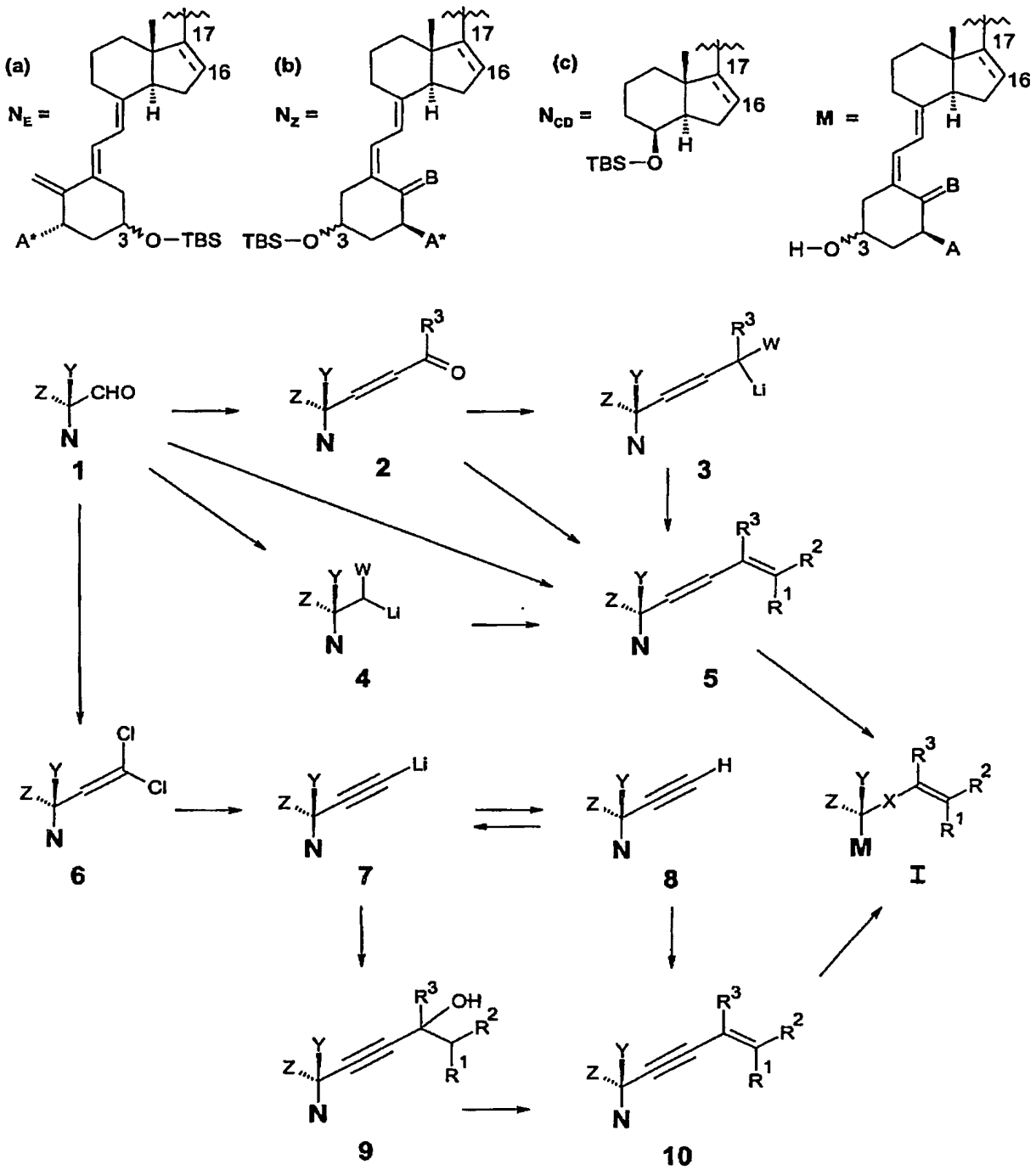
Prodrugs of the present invention may also be delivered by use of monoclonale antibodies as individual carriers to which the compound molecules are coupled.

In addition to the aforementioned ingredients, the formulations of a compound of formula I may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourant, surface active agents, thickeners, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

Furthermore, said formulations may also comprise other therapeutically active compounds normally used in the treatment of the above mentioned diseases. Examples of such compounds include phosphate binders, steroids and anti-proliferative agents.

In still another aspect, the invention relates to the use of a compound of formula I, optionally together with another therapeutically active compound in the manufacture of a medicament intended for the treatment of abnormal cell differentiation and/or cell proliferation, cancer, leukemia, mammary cancer, brain glial cancer, osteosarcoma, melanoma, myelofibrosis, psoriasis, primary hyperparathyroidism, s-HPT, s-HPT in association with renal failure, diabetes melitus, discoid and systemic lupus erythematosus, chronic dermatoses of autoimmune type, hypertension, acne, alopecia, skin aging, AIDS, neurodegenerative disorders, Alzheimer's disease, host versus graft and graft versus host reactions, rejections of transplants, steroid induced skin atrophy and osteroporosis, and for inducing osteogenisis. Said other therapeutically active compound may conveniently be selected from amongst, e.g. phosphate binders, steroids and anti-proliferative agents.

A compound of formula **I** may be prepared from the compounds **1** according to the reaction Scheme 1.


(a)
N_E =
(b)
N_Z =
(c)
N_{CD} =
M =
TBS–O
H–O
A*
A
B
17
16
H
3
1
2
3
4
5
6
7
8
9
10
I
CHO
Cl
Li
OH
W
X
M
N
Y
Z
R1
R2
R3

Scheme 1

5

The symbol * is used in this Scheme to indicate that the group A* in an intermediate compound may either be identical to the group A as found in the compound **I** (for example, fluorine in $\mathbf{N_Z}$), or alternatively may be a group that can be converted to this at any subsequent stage in the synthesis (for example, silyl ether protected hydroxyl in $\mathbf{N_Z}$). Although not formally indicated in this manner, the same situation may also apply for the variables R^1, R^2, R^3, Y, and Z on Scheme 1. Furthermore, the identity of **N** (i.e. $\mathbf{N_E}$, $\mathbf{N_Z}$, or $\mathbf{N_{CD}}$) and/or of one or more variable group(s) may change from intermediate to intermediate along the reaction sequence. However the actual identity will be apparent from the particular context. Note that while Cl and Li are atomic symbols (as are C, H, and O), the letter W is used as an abbreviation for a functional group or element that stabilises the organo-lithium species. The configuration (E or Z) of the double bond (to become X = ethylene in the final compounds **I**) is left unspecified in Scheme 1 (by drawing a linear arrangement) but is specified as and when required.

Starting materials of type **1** and certain examples of intermediates of type **2**, **4**, **6**, **7**, and **8** are described in the literature. The suffixes, **a**, **b** and **c**, identify the structure of the **N** group, as defined at the top of Scheme 1.

In outline, the suggested reactions, all well known to the synthetic organic chemist skilled in the art of vitamin D chemistry, are carried out as follows. (Standard abbreviations are used throughout this disclosure, e.g. Ac = acetyl; DCM = dichloromethane; Et = ethyl; Me = methyl; PDC = pyridinium dichromate; TBA = tetra(n-)butylammonium; TBS = t-butyldimethylsilyl; TMS = trimethylsilyl; Ts = p-tosyl; DIBAL = diisobutylaluminium hydride; THF = tetrahydrofurane.)

1 → 2 Wittig or Wadsworth-Emmons reaction [e.g. Wittig with $Ph_3P{=}CH{-}C(O)R^3$ (for R3 = H, via the R3 = OMe compound, from which it is derived by sequential DIBAL reduction and PDC or Dess-Martin periodinane oxidation).] The configuration of the double bond established in this reaction is usually E (small amounts of the Z compound can often be isolated however), but conditions can be selected to give an increased proportion of the Z compound, e.g. a modification of the Wadsworth-Emmons reaction using $(CF_3CH_2O)_2P(O)$-$CH_2C(O)OMe$. The E-configuration can alternatively be converted to Z by photoisomerisation at the stage of compound 2. Separation of the required isomer from a mixture of E and Z isomers can be performed at this or a later convenient stage.

1 → 4 For compounds with W = S(O2)Ph or W = SeMe, the methods have been described in the literature.

1 → 5 Wittig reaction with $Ph_3P{=}CH{-}C(R^3){=}CR^1R^2$. Separation of E and Z isomers established in this reaction can, if required, be performed now or a later convenient stage.

1 → 6 → 7 → 8 → 7 The dibromo-compound may be used instead of the shown dichloro-compound (**6**) in this part of a well-known reaction sequence for making alkynes.

2 → 3 For R^3= H (in **3**): Sequential DIBAL reduction [for R^3= OMe (or H) in **2** (see 1 → 2], conversion of the alcohol to a leaving group (e.g. Cl or OTs) which is then substituted to incorporate W (e.g. -P(O)Ph2 or -S(O2)Ph, either directly or via oxidation of the lower oxidation state -PPh2 or -SPh, all available as salts), and lithiation (e.g. with n-BuLi or LDA).

2 → 5 Wittig reaction e.g. with $Ph_3P=CR^1R^2$ or Wadsworth-Emmons reaction e.g. using $(EtO)_2P(O)-CR^1R^2$. If necessary, separation of 24-E and 24-Z isomers established in this reaction can be performed now or a later convenient stage.

3 → 5 Coupling reaction with a carbonyl compound: Horner reaction when W = P(O)Ph2; Julia reaction when W = S(O2)Ph (followed in the latter reaction by a reductive elimination of W together with the oxy-group). If necessary, separation of 24-E and 24-Z isomers established in this reaction can be performed now or a later convenient stage.

4 → 5 Coupling reaction with a carbonyl compound followed by elimination of W and the oxy-group. Separation of the required isomer from a mixture of E and Z isomers can be performed at this or a later convenient stage.

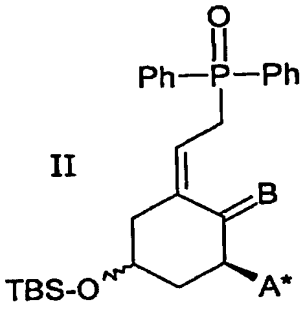
7 → 9 Coupling reaction with a carbonyl compound.

8 → 10 Palladium catalysed cross coupling with a terminal acetylene or with a vinyl or acetylenic derivative such as an halogenide (e.g. bromide). The reactions envisaged include those associated with the names of:- Heck, Suzuki, Cadiot-Chodkiewski, Negishi, Sonogashira, and Stille, to cite but a few.

9 → 10 Dehydration with Martin's sulfurane reagent.

5 or 10 → I "N → M": see below. In addition any necessary modification in A*, R^1, R^2, R^3, Y, and/or Z at some convenient stage.

N → M For N_{CD}: Sequential desilylation with HF to give the alcohol, oxidation with Dess-Martin periodinane to the ketone, and Horner-Wittig coupling with the lithio-derivative of the requisite known A-ring phosphine oxide of formula **II** to give N_Z. Then desilylation with HF or TBA-fluoride.



For N_E: Conversion to N_Z (B = CH_2) by triplet-sensitised photoisomerisation, then desilylation with HF or TBA-fluoride.

For N_Z: Desilylation with HF or TBA-fluoride.

The invention is further illustrated by the following Preparations and Examples:
The exemplified compounds **I** are listed in Table 1, whereas the starting materials and intermediates of general formulae **1** through **10** (Scheme 1) are listed in Table 2.

Table 1

Compound	Example Number	General Procedure	A	B	3-Configuration	16,17-bond	X	Y	Z	R1	R2	R3
1	1	9	OH	CH2	normal	single	E-ethylene	H	Me	Me	Me	H
2	2	9	OH	CH2	normal	single	Z-ethylene	H	Me	Me	Me	H
3	3	9	OH	CH2	normal	single	E-ethylene	Me	H	Me	Me	H
4	4	8	OH	CH2	normal	single	E-ethylene	H	Me	CH2-	-CH2	H
5	5	9	OH	CH2	normal	single	E-ethylene	Me	H	CH2-	-CH2	H
6	6	9	OH	CH2	normal	single	E-ethylene	H	Me	CH2-	-(CH2)2	H
7	7	9	OH	CH2	normal	single	E-ethylene	Me	H	CH2-	-(CH2)2	H
8	18	8	OH	CH2	normal	single	E-ethylene	Me	H	Br	Br	H
9	8	9	OH	CH2	normal	single	E-ethylene	H	Me	Me	CH2OH	H
10	9	9	OH	CH2	normal	single	E-ethylene	Me	H	Me	CH2OH	H
11	10	9	OH	CH2	normal	single	E-ethylene	H	Me	CH2OH	Me	H
12	11	9	OH	CH2	normal	single	E-ethylene	Me	H	CH2OH	Me	H
13	12	9	OH	CH2	normal	single	E-ethylene	H	Me	Me	C(OH)Et2	H
14	13	9	OH	CH2	normal	single	E-ethylene	H	Me	H	H	cyclo-propyl
15	14	8	OH	CH2	normal	single	ethynylene	H	Me	Me	Me	H
16	15	8	OH	CH2	normal	single	ethynylene	Me	H	C(OH)Me2	bond	bond
17	16	8	OH	CH2	normal	single	ethynylene	H	Me	C(OH)Et2	bond	bond
18	17	8	OH	CH2	normal	single	ethynylene	Me	H	C(OH)Et2	bond	bond

19		8	OH	CH2	normal	single	ethynylene	H	Me	CMe3	bond	bond
20		8	OH	CH2	normal	single	ethynylene	Me	H	CMe3	bond	bond
21	19		F	CH2	normal	single	E-ethylene	H	Me	Me	Me	H
22	20		OH	H2	normal	single	E-ethylene	H	Me	Me	Me	H
23	21		OH	CH2	epi	single	E-ethylene	H	Me	Me	Me	H
24	22		OH	CH2	normal	double	E-ethylene	Me	H	Me	Me	H
25	23	8	OH	CH2	normal	single	E-ethylene	H	Me	CF3	CF3	H
26			H	CH2	normal	single	E-ethylene	H	Me	Me	CH2OH	H

Table 2

Entry	Com-pound number	Type (Scheme 1)	Prepar-ation Number	Gen Proc	A*	B	3-Configu-ration	16,17-bond	Y	Z	Ethylene configu-ration (X)	R1	R2	R3	W
1	101	1a			O-TBS		normal	single	H	Me					
2	102	1c						single	H	Me					
3	103	1a			O-TBS		normal	single	Me	H					
4	104	1a			O-TBS		normal	double	Me	H					
5	202	2a			O-TBS		normal	single	H	Me				H	
6	203	2a			O-TBS		normal	single	Me	H				H	

7	204	2a			O-TBS		normal	single	H	Me	E			cyclo-propyl	
8	205	2a		1	O-TBS		normal	single	H	Me	E			Me	
9	206	2c						single	H	Me				H	
10	301	3a			O-TBS		normal	single	H	Me	E			H	SO2-Ph
11	302	3a			O-TBS		normal	single	H	Me	E			H	P(O)Ph2
12	401	4a			O-TBS		normal	single	H	Me				H	SO2-Ph
13	402	4a			O-TBS		normal	single	H	Me				H	P(O)Ph2
14	403	4a			O-TBS		normal	single	H	Me				H	SeMe
15	501	5a	1	1	O-TBS		normal	single	H	Me	E	Me	Me	H	
16	502	5a	8		O-TBS		normal	single	H	Me	Z	Me	Me	H	
17	503	5a	3	1	O-TBS		normal	single	Me	H	E	Me	Me	H	
18	504	5a	4	1	O-TBS		normal	single	H	Me	E	CH2-	-CH2	H	
19	505	5a	5	1	O-TBS		normal	single	Me	H	E	CH2-	-CH2	H	
20	506	5a	6	1	O-TBS		normal	single	H	Me	E	CH2-	-(CH2)2	H	
21	507	5a	7	1	O-TBS		normal	single	Me	H	E	CH2-	-(CH2)2	H	
22	508	5a	9	2	O-TBS		normal	single	H	Me	E	Me	CO2Et	H	
23	509	5a	9	2	O-TBS		normal	single	H	Me	E	CO2Et	Me	H	
24	510	5a	11	3	O-TBS		normal	single	H	Me	E	Me	CH2OH	H	
25	511	5a	12	3	O-TBS		normal	single	H	Me	E	CH2OH	Me	H	
26	512	5a	10	2	O-TBS		normal	single	Me	H	E	Me	CO2Et	H	
27	513	5a	10	2	O-TBS		normal	single	Me	H	E	CO2Et	Me	H	
28	514	5a	13	3	O-TBS		normal	single	Me	H	E	Me	CH2OH	H	
29	515	5a	14	3	O-TBS		normal	single	Me	H	E	CH2OH	Me	H	
30	516	5a	15	4	O-TBS		normal	single	H	Me	E	Me	C(OH)	H	

													Et2		
31	517	5a	16		O-TBS		normal	single	H	Me	E	H	H	cycl o-prop yl	
32	518	5a	17		O-TBS		normal	single	Me	H	E	Br	Br	H	
33	534	5a			O-TBS		normal	single	H	Me	E	CF3	CF3	H	
34	519	5b	101	7	O-TBS	CH2	normal	single	H	Me	E	Me	Me	H	
35	520	5b	114	7	O-TBS	CH2	normal	single	Me	H	E	Br	Br	H	
36	521	5b	102	7	O-TBS	CH2	normal	single	H	Me	Z	Me	Me	H	
37	522	5c	2	1				single	H	Me	E	Me	Me	H	
38	523	5b	103	7	O-TBS	CH2	normal	single	Me	H	E	Me	Me	H	
39	524	5b	104	7	O-TBS	CH2	normal	single	H	Me	E	CH2-	-CH2	H	
40	525	5b	105	7	O-TBS	CH2	normal	single	Me	H	E	CH2-	-CH2	H	
41	526	5b	106	7	O-TBS	CH2	normal	single	H	Me	E	CH2-	-(CH2)2	H	
42	527	5b	107	7	O-TBS	CH2	normal	single	Me	H	E	CH2-	-(CH2)2	H	
43	528	5b	108	7	O-TBS	CH2	normal	single	H	Me	E	Me	CH2OH	H	
44	529	5b	109	7	O-TBS	CH2	normal	single	H	Me	E	CH2OH	Me	H	
45	530	5b	110	7	O-TBS	CH2	normal	single	Me	H	E	Me	CH2OH	H	
46	531	5b	111	7	O-TBS	CH2	normal	single	Me	H	E	CH2OH	Me	H	
47	532	5b	112	7	O-TBS	CH2	normal	single	H	Me	E	Me	C(OH) Et2	H	
48	533	5b	113	7	O-TBS	CH2	normal	single	H	Me	E	H	H	cycl o-prop yl	
49	535	5b		7	O-TBS	CH2	normal	single	H	Me	E	CF3	CF3	H	
50	601	6a			O-TBS		normal	single	H	Me					

51	602	6a			O-TBS		normal	single	Me	H					
52	701	7a	18, 19	5	O-TBS		normal	single	H	Me					
53	702	7a	20	5	O-TBS		normal	single	Me	H					
54	801	8a	19	5	O-TBS		normal	single	H	Me					
55	802	8a	20	5	O-TBS		normal	single	Me	H					
56	901	9a	18	5	O-TBS		normal	single	H	Me		Me	Me	H	
57	1001	10a	18	5	O-TBS		normal	single	H	Me		Me	Me	H	
58	1002	10b	115	7	O-TBS	CH2	normal	single	H	Me		Me	Me	H	
59	1003	10a	21	6	O-TBS		normal	single	Me	H		C(OH)Me2	bond	bond	
60	1004	10b	116	7	O-TBS	CH2	normal	single	Me	H		C(OH)Me2	bond	bond	
61	1005	10a	22	6	O-TBS		normal	single	H	Me		C(OH)Et2	bond	bond	
62	1006	10b	117	7	O-TBS	CH2	normal	single	H	Me		C(OH)Et2	bond	bond	
63	1007	10a	23	6	O-TBS		normal	single	Me	H		C(OH)Et2	bond	bond	
64	1008	10b	118	7	O-TBS	CH2	normal	single	Me	H		C(OH)Et2	bond	bond	
65	1009	10a		6	O-TBS		normal	single	H	Me		CMe3	bond	bond	
66	1010	10b		7	O-TBS	CH2	normal	single	H	Me		CMe3	bond	bond	
67	1011	10a		6	O-TBS		normal	single	Me	H		CMe3	bond	bond	
68	1012	10b		7	O-TBS	CH2	normal	single	Me	H		CMe3	bond	bond	

PREPARATIONS AND EXAMPLES

Reactions were routinely (unless otherwise noted) run by stirring under an argon atmosphere, with additions of reagent (liquid or in solution) occurring drop wise via a syringe. As standard work-up procedure, the organic layer was separated, washed sequentially with water and saturated sodium chloride solution, dried over anhydrous magnesium sulphate, and concentrated in vacuo to give a crude product, which was then purified by chromatography. All preparative and analytical (TLC) chromatography was performed on silica gel using a gradient from 1% to 50% ether (i.e. diethyl ether) in petroleum ether as eluent, or from 30% ethyl acetate in petroleum ether to pure ethyl acetate. In the General Procedures, the variable entries are indented (on separate lines) and then listed in the specific Preparations, together with details if needed on any deviations from the General Procedure that were actually employed. However the proportional scaling of the quantities of non-variable reagents and solvents to the molar quantities specified in each Preparation is taken for granted and thus not considered a deviation requiring explicit details.

Compounds were characterised spectroscopically: For ^{1}H nuclear magnetic resonance spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified, for deuteriochloroform solutions relative to internal tetramethylsilane (added, $\delta_H = 0.00$) or chloroform (residual, $\delta_H = 7.25$) or deuteriochloroform ($\delta_C = 76.81$ for 13C NMR). The value for a multiplet (^{1}H-NMR), either defined [doublet (d), triplet (t), quartet (q)] or not (m) at the approximate mid point is given unless a range is quoted (s = singlet, b = broad). In some cases, only selected, characteristic signals may be reported for the intermediate compounds i.e. those of Table 2.

General Procedure 1 (Preparations 1-7) **[2 → 5]**

To a solution or suspension, maintained at about -70 °C, of the

alkyl-triphenylphosphonium salt (7 mmol)

in dry THF (50 ml) was added n-butyl-lithium (1.6M in hexanes, 4.36 ml, 7 mmol). The temperature of the mixture was then allowed to rise to 0°C for 20 min, after which recooling at -70 °C was resumed for the addition of

compound **2** (4 mmol),

dissolved in dry THF (8 ml). After 30 minutes at the same temperature, slow warming up, and 70 min at room temperature, the mixture was partitioned between saturated ammonium chloride solution and ethyl acetate, and worked up as standard to give compound **5**.

Preparation 1: Compound 501

isopropyl-triphenylphosphonium iodide (3.16 g, 7.3 mmol)

202 (2.39 g)

Isolation from the crude product by direct crystallisation from methanol, omitting the chromatography step.

501: δ_C 153.5, 143.1, 138.1, 135.2, 132.5, 125.1, 124.1, 121.5, 116.3, 106.4, 70.0, 67.1, 56.3, 56.2, 45.7, 43.8, 40.4, 40.3, 36.4, 28.8, 27.7, 25.7, 25.6, 23.3, 22.0, 20.6, 18.1, 18.0, 17.9, 12.1, -4.9, -5.1 ppm.

Preparation 2: Compound 522

isopropyl-triphenylphosphonium iodide (1.55 g, 3.6 mmol)

206 (Prepared from 102 analogously to the described preparation of 202 from 101 in WO9100855) (0.7 g, 2 mmol)

522: δ_C 138.5, 132.3, 125.1, 123.8, 69.3, 56.4, 52.9, 42.0, 40.5, 39.7, 34.3, 29.2, 25.7, 25.6, 22.8, 20.3, 18.0, 17.8, 17.5, 13.8, -5.0, -5.3 ppm.

Preparation 3: Compound 503

isopropyl-triphenylphosphonium iodide (1.47 g, 3.4 mmol)

203 (1 g, 1.67 mmol)

Chromatography: 2% ether in petroleum ether

503: δ_C 153.4, 143.3, 138.5, 135.1, 132.3, 125.1, 124.0, 121.6, 116.1, 106.4, 70.1, 67.0, 56.7, 56.1, 45.8, 43.8, 40.6, 39.6, 36.4, 28.8, 27.1, 25.7, 25.7, 25.6, 23.3, 21.9, 21.3, 18.1, 17.9, 12.1, -4.9, -5.1 ppm.

Preparation 4: Compound 504

cyclopropyl-triphenylphosphonium bromide (0.76 g, 2 mmol)

202 (0.60 g, 1 mmol)

Chromatography: 5% ether in petroleum ether

504: δ_H 6.45 (d, J=12Hz, 1H), 6.33 (bd, J=10Hz, 1H), 6.12 (dd, J=15Hz, J=10Hz, 1H), 5.81 (d, J=12Hz, 1H), 5.55 (dd, J=9Hz, J=15Hz, 1H), 4.97 (m, 1H), 4.93 (m, 1H), 4.53 (m, 1H), 4.23 (m, 1H), 2.86 (m, 1H), 2.55 (dd, 1H), 2.30 (bd, 1H), 2.20 - 1.15 (m, 14H), 1.15 - 1.0 (m, 14H), 1.07 (d, J=7Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.57 (s, 3H), 0.05 (m, 12H) ppm.

Preparation 5: Compound 505

cyclopropyl-triphenylphosphonium bromide (1.53 g, 4 mmol)

203 (0.56 g, 0.93 mmol)

Chromatography: 5% ether in petroleum ether

505: δ_H 6.44 (d, J=11.4Hz, 1H), 6.35 (bd, J=10.3Hz, 1H), 6.08 (dd, J=10.3Hz, J=15.3, 1H), 5.81 (d, J=11.4Hz, 1H), 5.55 (dd, J=9.5Hz, J=15.3, 1H), 4.97 (bt, 1H), 4.93 (bt, 1H), 4.52 (m, 1H), 4.21 (m, 1H), 2.84 (m, 1H), 2.54 (dd, J=5.3Hz, J=14.5Hz, 1H), 2.31 (bd, J=13.7Hz, 1H), 2.2 - 1.0 (m, 18H), 0.97 (d, J=6.5Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.52 (s, 3H), 0.05 (s, 12H) ppm.

Preparation 6: Compound 506

cyclobutyl-triphenylphosphonium bromide (0.80g, 2 mmol)

202 (0.60 g, 1 mmol)

Chromatography: 1% ether in petroleum ether

506: δ_C 153.5, 143.1, 142.5, 137.1, 135.2, 123.6, 121.5, 120.8, 116.3, 106.4, 70.0, 67.0, 56.3, 56.2, 45.7, 43.8, 40.3, 40.3, 36.4, 31.1, 29.7, 28.7, 27.7, 25.7, 25.6, 23.3, 22.0, 20.5, 18.1, 17.9, 17.0, 12.0, -4.9, -5.0, -5.1 ppm.

Preparation 7: Compound 507

cyclobutyl-triphenylphosphonium bromide (1.33 g, 3.34 mmol)

203 (1 g, 1.67 mmol)

Chromatography: 1% ether in petroleum ether

507: δ_C 153.4, 143.3, 142.4, 137.4, 135.1, 123.6, 121.6, 120.9, 116.1, 106.4, 70.1, 67.0, 56.8, 56.1, 45.8, 43.8, 40.6, 39.6, 36.4, 31.1, 29.7, 28.8, 27.1, 25.7, 25.6, 23.3, 21.9, 21.3, 18.1, 17.9, 16.9, 12.1, -4.9, -5.1 ppm.

Preparation 8: Compound 502

To a solution, maintained at about -70 °C, of the lithio-derivative 403 (entry 13) (1 mmol) in dry THF (5 ml) (from 0.42 g, 0,56 mmol of the seleno-acetal derivative of 101) was added dropwise the side chain building block 3-methyl-crotonaldehyde (0.10 g, 1.2 mmol). After stirring at the same temperature for 30 min, the reaction was quenched with wet THF and the mixture partitioned between ether and water and to give the intermediate adduct as a mixture of diastereoisomers. To a solution of this, maintained at about 5 °C, in dry DCM (15 ml) and triethylamine (2 ml) was added methanesulphonyl chloride (1.5 mmol). After stirring at the same temperature for 30 min, the reaction mixture was partitioned between ether and water. The standard work-up gave compound 502: δ_C 153.5, 143.1, 136.0, 135.2, 134.4, 121.7, 121.5, 120.4, 116.3, 106.4, 70.0, 67.0, 56.5, 56.3, 45.7, 43.8, 40.4, 40.3, 36.4, 28.8, 27.3, 25.7, 25.6, 23.4, 22.0, 20.6, 18.0, 17.9, 12.2, -4.9, -5.0, -5.1 ppm.

General Procedure 2 (Preparations 9, 10) [**2** → **5**]

To a solution, maintained at about 20 °C, of

compound **2** (0.76 mmol)

in DCM (5 ml) was added triethyl 2-phosphonopropionate (0.45 g, 1.9 mmol), 50% aqueous NaOH solution (5 ml), and TBA hydrogen sulphate (0.11 g). After vigorous stirring for 105 min, the reaction mixture partitioned between water and ethyl acetate. Standard work-up (chromatography 2%-5% ethyl acetate in petroleum ether as eluent) gave compounds **5**.

Preparation 9: Compound 508 and 509

compound 202 (0.46 g)

First eluted product: compound 509: δ_C 167.6, 153.5, 147.6, 142.8, 141.1, 135.3, 125.3, 123.8, 121.5, 116.4, 106.3, 70.0, 67.0, 59.9, 56.2, 55.8, 45.8, 43.8, 40.3, 40.3, 36.4, 28.7, 27.5, 25.7, 25.6, 23.3, 22.1, 20.4, 20.0, 18.1, 17.9, 14.1, 12.1, -5.0, -5.1 ppm;
Second eluted product: compound 508: δ_C 168.5, 153.5, 148.7, 142.7, 138.7, 135.4, 124.9, 123.5, 121.5, 116.4, 106.4, 70.0, 67.0, 60.2, 56.1, 55.7, 45.8, 43.8, 40.8, 40.2, 36.4, 28.7, 27.5, 25.7, 25.6, 23.3, 22.1, 20.0, 18.1, 17.9, 14.1, 12.4, 12.1, -5.0, -5.1 ppm.

Preparation 10: Compound 512 and 513

compound 203 (1 g, 1.68 mmol)

First eluted product: compound 513: δ_C 167.6, 153.4, 148.1, 143.0, 140.8, 135.2, 125.2, 123.8, 121.5, 116.2, 106.4, 70.0, 67.0, 59.9, 56.6, 56.0, 45.8, 43.8, 40.7, 39.6, 36.4, 28.7, 27.0, 25.7, 25.6, 23.2, 21.8, 20.6, 20.5, 18.1, 17.9, 14.1, 12.1, -4.9, -5.1 ppm;
Second eluted product: compound 512: δ_C 168.5, 153.4, 149.3, 142.9, 138.5, 135.3, 124.9, 123.4, 121.5, 116.3, 106.5, 70.1, 67.0, 60.2, 56.5, 56.0, 45.7, 43.8, 41.1, 39.6, 36.4, 28.7, 27.0, 25.7, 25.6, 23.2, 21.8, 20.7, 18.0, 17.9, 14.2, 12.4, 12.2, -5.0, -5.1, -5.1 ppm.

General Procedure 3 (Preparations 11 to 14)

To a solution, maintained at about -70 °C, of the

ester **5** (0.34 mmol)

in dry THF (5 ml) was added DIBAL (1M in hexanes, 1 ml, 1 mmol). After 30 min at the same temperature, the temperature of the mixture was then allowed to rise to -20°C over 1 h, after which recooling at -70 °C was resumed for the addition of methanol (0.5 ml) to quench the reaction. The mixture was then partitioned between water and ethyl acetate, and worked up as standard to give the alcohol **5**.

Preparation 11: Compound 510

compound 508 (0.23 g)

Compound 510: δ_C 153.5, 142.9, 141.2, 135.3, 134.5, 125.4, 123.3, 121.5, 116.3, 106.4, 70.0, 68.6, 67.0, 56.2, 56.1, 45.7, 43.8, 40.4, 40.3, 36.4, 28.7, 27.7, 25.7, 25.6, 23.3, 22.0, 20.4, 18.1, 17.9, 13.9, 12.1, -4.9, -5.1 ppm.

Preparation 12: Compound 511

compound 509 (0.18 g, 0.26 mmol)

Compound 511: δ_C 153.5, 142.9, 140.8, 135.3, 134.0, 128.3, 122.7, 121.5, 116.3, 106.4, 70.1, 67.0, 61.7, 56.2, 56.1, 45.7, 43.8, 40.3, 36.4, 28.7, 27.6, 25.7, 25.6, 25.4, 23.3, 22.0, 21.2, 20.3, 18.0, 17.9, 12.1, -5.0, -5.1 ppm.

Preparation 13: Compound 514

compound 512 (0.36 g, 0.53 mmol)

Compound 514: δ_C 153.4, 143.1, 141.6, 135.1, 134.3, 125.4, 123.2, 121.5, 116.2, 106.5, 70.1, 68.6, 67.0, 56.7, 56.1, 45.8, 43.8, 40.7, 39.6, 36.4, 28.8, 27.1, 25.7, 25.6, 23.2, 21.9, 21.1, 18.0, 17.9, 13.9, 12.1, -5.0, -5.1 ppm.

Preparation 14: Compound 515

compound 513 (0.23 g)

Compound 515: δ_C 153.4, 143.1, 141.3, 135.2, 133.9, 128.3, 122.6, 121.5, 116.2, 106.5, 70.1, 67.0, 61.7, 56.7, 56.1, 45.8, 43.8, 40.6, 39.6, 36.4, 28.8, 27.1, 25.7, 25.6, 23.2, 21.9, 21.2, 21.0, 18.0, 17.9, 12.1, -4.9, -5.1 ppm.

General Procedure 4 (Preparation 15)

To a solution, maintained at about -70 °C, of the

ester **5** (0.6 mmol)

in dry THF (5 ml) was added

the alkyl-lithium

After 1 h at the same temperature, the reaction was quenched with methanol (0.5 ml), and the mixture partitioned between ether and water. Standard work-up gave the alcohol **5**.

Preparation 15: Compound 516

compound 508 (0.4 g)

ethyl-lithium (0.8 M in diethyl ether, 2 ml)

Compound 516: δ_C 153.5, 143.0, 140.1, 137.3, 135.2, 124.4, 123.8, 121.5, 116.3, 106.4, 78.2, 70.1, 67.0, 56.3, 56.2, 45.8, 43.8, 40.4, 40.3, 36.4, 31.6, 28.8, 27.6, 25.7, 25.6, 23.3, 22.0, 20.4, 18.1, 17.9, 13.3, 12.1, 7.4, -4.9, -5.1 ppm.

Preparation 16: Compound 517

To a solution/suspension, maintained at about 5 °C, of compound 204 (0.32 g, 0.5 mmol) and methyl-triphenylphosphonium bromide (0.59 g, 1.57 mmol) in dry THF (5 ml) was added potassium tert-butoxide (1M solution in THF, 1.4 ml).

After 2 h at the same temperature, the mixture was partitioned between water and ether, and worked up as standard to give Compound 517, recrystallised from ether-methanol: δ_C 153.5, 147.6, 143.0, 136.8, 135.3, 129.6, 121.5, 116.3, 110.3, 106.4, 70.0, 67.0, 56.3, 45.8, 43.8, 40.3, 40.2, 36.4, 28.8, 27.5, 25.7, 25.6, 23.3, 22.0, 20.4, 18.1, 17.9, 12.6, 12.1, 5.3, 5.2, -5.0, -5.1 ppm.

Preparation 17: Compound 518

Tetrabromomethane (288 mg, 0.87 mmol) was dissolved in dry THF (3.6 ml). Triphenylphosphine (456 mg, 1.74 mmol) was added and the reaction mixture stirred for 30 minutes at room temperature. A solution of Compound 203 (261 mg ; 0.435 mmol) and triethylamine (0.06 ml ; 0.43 mmol) in THF (3.2 ml) was added. The reaction mixture was stirred for 90 minutes at room temperature, quenched with water (15 ml) and filtered through Decalite filter aid. The filter was washed with pentane (2 x 25 ml). The filtrate was extracted with water (3 x 15 ml) and saturated aqueous sodium chloride (15 ml), dried and concentrated in vacuo. The residue was purified by chromatography (0.5% ether in petroleum ether). 518: δ_C 153.4, 145.7, 142.8, 137.0, 135.3, 124.6, 121.5, 116.3, 106.5, 88.1, 70.1, 67.0, 56.4, 56.0, 45.7, 43.8, 40.8, 39.6, 36.4, 29.5, 28.7, 27.0, 25.7, 25.6, 25.4, 23.1, 21.8, 20.5, 18.1, 17.9, 12.1, -5.0, -5.1 ppm.

General Procedure 5 (Preparations 18, 19, 20)

[6 → 7 → 9 → 10, including 6 → 7→ 8]

To a solution, maintained at about -70 °C, of the dichloro-compound

6 (1 mmol)

in dry THF (5 ml) was added n-butyl-lithium (1.33 ml, 1.5M in hexanes, 2 molar eq.). The temperature of the mixture was then allowed to rise to 0°C momentarily to ensure effective conversion to the intermediate lithio-derivative **7**. Quenching by partitioning between saturated ammonium chloride solution and ether, and work up at this stage mixture gave

the compound **8**. Alternatively recooling of the solution of **7** at -70 °C was resumed, and addition of the

carbonyl compound (1.5 mmol),

was made. After 30 minutes at the same temperature and slow warming up to room temperature, the mixture was partitioned between saturated ammonium chloride solution and ether, and worked up as standard to give compound **9**.

To a solution of, maintained at about 5 °C, of this intermediate alcohol

9 (ca. 0.4 mmol)

in dry dichloromethane (8 ml) was added Martin's sulfurane (0.54 g, 2 molar equiv.). After stirring at the same temperature for 1 h, the reaction mixture was partitioned between ether and 20% sodium hydroxide solution. Standard work-up gave the Product **10**.

Preparation 18: Compound 1001 via Intermediate 701 and Compound 901

601 (0.62 g, 0.97 mmol)

isobutyraldehyde (0.13 ml)

901: δ_C 153.5, 142.6, 135.4, 121.4, 116.4, 106.4, 90.4, 80.3, 70.0, 68.0, 67.0, 55.9, 55.8, 45.6, 43.8, 39.5, 36.4, 34.5, 28.7, 27.6, 26.3, 25.7, 25.6, 23.1, 22.0, 21.4, 18.1, 18.0, 17.9, 17.2, 12.4, -5.0, -5.1 ppm.

901 (0.27 g)

The product was further purified by crystallisation from ether-methanol.

1001: δ_C 153.4, 146.0, 142.8, 135.3, 121.5, 116.4, 106.5, 105.4, 96.5, 78.9, 70.1, 67.0, 56.1, 56.0, 45.6, 43.8, 39.6, 36.4, 28.7, 28.4, 26.4, 25.7, 25.6, 24.4, 23.1, 22.1, 21.6, 20.6, 18.1, 17.9, 12.3, -5.0, -5.1, -5.1 ppm.

Preparation 19: Compound 801 via Intermediate 701

601 (0.64 g)

801: δ_C 153.4, 142.6, 135.4, 121.4, 116.5, 106.5, 89.0, 70.1, 68.4, 67.0, 55.9, 55.5, 45.6, 43.8, 39.6, 36.4, 28.7, 27.6, 26.4, 25.7, 25.6, 23.1, 22.0, 21.2, 18.1, 17.9, 12.1, -4.9, -5.1, -5.1 ppm.

Preparation 20: Compound 802 via Intermediate 702

602 (0.66 g)

802: δ_C 153.4, 142.9, 135.3, 121.5, 116.3, 106.5, 89.1, 70.1, 69.0, 67.1, 56.0, 55.4, 45.8, 43.8, 39.5, 36.4, 28.8, 27.3, 25.7, 25.6, 23.2, 21.7, 20.8, 18.1, 17.9, 12.1, -4.9, -5.1, -5.1 ppm.

1-Bromo-3-hydroxy-3-ethyl-pentyne

To a solution of 3-hydroxy-3-ethyl-1-pentyne (20 mmol) in dry THF (40 ml) at room temperature was added n-butyl-lithium (42 mmol, 1.6M in hexanes) during 10 minutes. After stirring for 30 minutes, the solution was cooled to -40°C and a solution of bromine (1.13 ml, 3.52 g, 22 mmol) in dry THF (20 ml), also cooled to -40°C, was added, during 20 minutes, followed by re-heating to 25°C, during about 1 hour. Standard work-up after addition of ether and water (chromatography: 0% to 10% ether in petroleum ether) gave the title compound.

1-Bromo-3-hydroxy-3-methyl-1-butyne

When 3-hydroxy-3-methyl-1-butyne was used as starting material in the above preparation the product was 1-bromo-3-hydroxy-3-methyl-1-butyne. This was also prepared from 3-hydroxy-3-methyl-1-butyne by treatment at room temperature of an acetone solution with silver nitrate (0.3 eq.) and then, after 20 min, N-bromosuccinimide (1 molar equiv.). After 12 h ether was added, the solution filtered, and the filtrate worked-up as standard to give an oil that was distilled (b.p. 67 ^{0}C /18 mmHg): δ_C 31.0, 31.0, 42.6, 66.1, 84.3 ppm.

General Procedure 6 (Preparations 21 to 23) [8 → 10]

To a solution, maintained at about 25 °C, in dry pyrrolidine (5 ml) of the compound

8 (0.2 mmol)

was added the

side chain building block (0.8 mmol; 4 molar equiv.),

CuI (4 mg; 0.1 molar equiv.) and bis-triphenylphosphine-palladium dichloride (7 mg; 0.05 molar equiv.). After stirring at the same temperature for 17 h, the reaction mixture was partitioned between ether and saturated ammonium chloride solution and worked up as standard to give **10**.

Preparation 21: Compound 1003

802 (66 mg, 0.11 mmol)

1-Bromo-3-hydroxy-3-methyl-1-butyne (75 mg)

1003: δ_C 153.4, 142.7, 135.4, 121.4, 116.3, 106.5, 85.6, 80.4, 70.1, 67.2, 67.0, 65.4, 65.2, 55.8, 55.4, 45.7, 43.8, 39.2, 36.4, 31.0, 28.8, 28.0, 27.2, 25.7, 25.6, 23.3, 21.7, 20.3, 18.1, 17.9, 12.2, -5.0, -5.1, -5.1 ppm.

Preparation 22: Compound 1005

801 (114 mg)

1-bromo-3-hydroxy-3-ethyl-1-pentyne

1005: δ_C 153.4, 142.4, 135.5, 121.4, 116.5, 106.5, 85.0, 78.5, 72.5, 70.1, 69.3, 67.0, 64.9, 55.8, 55.6, 45.7, 43.7, 39.5, 36.4, 34.1, 28.6, 28.3, 26.3, 25.7, 25.6, 23.1, 22.0, 20.7, 18.1, 17.9, 12.2, 8.3, -5.0, -5.1, -5.1 ppm.

Preparation 23: Compound 1007

802 (118 mg)

1-bromo-3-hydroxy-3-ethyl-1-pentyne

1007: δ_C 153.4, 142.7, 135.4, 121.4, 116.3, 106.5, 85.0, 78.8, 72.5, 70.1, 69.2, 67.0, 65.4, 55.8, 55.4, 45.7, 43.8, 39.2, 36.4, 34.1, 28.8, 27.9, 27.1, 25.7, 25.6, 23.3, 21.7, 20.2, 18.1, 17.9, 12.2, 8.3, -5.0, -5.1, -5.1 ppm.

General Procedure 7 (Preparations 101-118)

a → b (B = CH_2)

To a solution of the 5E-Vitamin D

compound of type **a** (0.1 mmol),

a triplet-sensitiser (0.01 g),

and triethylamine (0.05 ml) in

a solvent (5 ml)

in a Pyrex flask was irradiated with light from a high pressure ultraviolet lamp, type TQ180Z2 (Hanau) at about 20 °C for 30 minutes (the time was scaled-up proportionally according to the amount of compound **a**). The reaction mixture (after filtering when anthracene was used) was partially concentrated in vacuo and purified by chromatography to give the product compound of type **b**.

Preparation 101: Compound 519

501 (1.29 g, 2.06 mmol)

anthracene (0.65 g)

DCM (100 ml)

A TQ718Z2 lamp was used for 35 min.

519: δ_H 6.23 (d, 1H), 6.13 (dd, 1H, J=11.1 Hz and 14.9 Hz), 6.00 (d, 1H), 5.75 (d, 1H, J=11.1 Hz), 5.40 (dd, 1H, J=8.8 Hz and 14.9 Hz), 5.17 (m, 1H), 4.85 (m, 1H), 4.36 (m, 1H), 4.18 (m, 1H), 2.82 (m, 1H), 2.44 (dd, 1H), 2.21 (dd, 1H), 2.11 (m, 1H), 1.74 (bs, 3H), 1.73 (bs, 3H), 2.03 - 1.14 (m, 13H), 1.04 (d, 3H), 0.87 (s, 18H), 0.55 (s, 3H), 0.05 (m, 12H) ppm.

Preparation 102: Compound 521

502 (63 mg)

9-acetyl-anthracene

DCM

521: δ_H In agreement with structure.

Preparation 103: Compound 523

503 (0.38 g)

anthracene (0.32 g)

DCM

Chromatography: 0.5% ether in petroleum ether

523: δ_H 6.22 (d, J=11.2Hz, 1H), 6.11 (dd, J=14.9Hz, J=10.7Hz, 1H), 6.00 (d, J=11.2Hz, 1H), 5.76 (d, J=10.7Hz, 1H), 5.41 (dd, J=9.6Hz, J=14.9Hz, 1H), 5.17 (m, 1H), 4.86 (m, 1H), 4.36 (m, 1H), 4.18 (m, 1H), 2.80 (m, 1H), 2.43 (dd, J=3.8Hz, J=13.0Hz, 1H), 2.20 (dd, J=7.5Hz, J=13.0Hz, 1H), 2.15 - 1.0 (m, 14H), 1.75 (bs, 3H), 1.72 (bs, 3H), 0.93 (d, J=6.5Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.49 (s, 3H), 0.05 (bs, 12H) ppm.

Preparation 104: Compound 524

504 (61 mg)

anthracene (0.05 g)

DCM

Chromatography: 0 - 2% ether in petroleum ether

524: δ_H 6.33 (bd, J=10.3Hz, 1H), 6.22 (d, J=11.2Hz, 1H), 6.11 (dd, J=10.3Hz, J=15.3Hz, 1H), 6.01 (d, J=11.2Hz,1H), 5.55 (dd, J=15.3Hz, J=8.8Hz, 1H), 5.17 (bs, 1H), 4.86 (bs, 1H), 4.18 (m, 1H), 2.81 (m, 1H), 2.44 (m, 1H), 2.25 - 1.0 (m, 20H), 1.06 (d, J=6.8Hz, 3H), 0.87 (s, 18H), 0.55 (s, 3H), 0.05 (bs, 12H) ppm.

Preparation 105: Compound 525

505 (0.24 g)

anthracene (0.23 g)

DCM

Chromatography: 0 - 2% ether in petroleum ether

525: δ_H 6.35 (bd, J=10.3Hz, 1H), 6.22 (bd, J=11.5Hz, 1H), 6.08 (dd, J=10.3Hz, J=15.4Hz, 1H), 6.00 (d, J=11.5Hz, 1H), 5.55 (dd, J=9.4Hz, J=15.4Hz, 1H), 5.17(bd, 1H), 4.86 (bd, 1H), 4.36 (m, 1H), 4.18 (m, 1H), 2.80 (bd, J=12.2Hz, 1H), 2.43 (dd, J=3.6, J=13.0Hz, 1H), 2.20 (dd, J=7.3Hz, J=13.0Hz, 1H), 2.15 - 1.0 (m, 18H), 0.97 (d, J=6.8Hz, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.50 (s, 3H), 0.05 (bs, 12H) ppm.

Preparation 106: Compound 526

506 (0.4 g)
anthracene (0.34 g)
DCM

Chromatography: 0.5% ether in petroleum ether

526: δ_H 6.22 (d, J=11.2Hz, 1H), 6.00 (d, J=11.2Hz, 1H), 5.84 (dd, J=15Hz, J=10.7Hz, 1H), 5.65 (m, 1H), 5.34 (dd, J=15Hz, J=8.7Hz, 1H), 5.17 (bs, 1H), 4.85 (bs, 1H), 4.36 (m, 1H), 4.18 (m, 1H), 2.69 (m, 5H), 2.44 (m, 1H), 2.25 - 1.10 (m, 17H), 1.03 (d, J=6.7Hz, 3H), 0.87 (s, 18H), 0.54 (s, 3H), 0.05 (bs, 12H) ppm.

Preparation 107: Compound 527

507 (0.38 g)
anthracene (0.32 g)
DCM

Chromatography: 0.5% ether in petroleum ether

527: δ_C 148.2, 142.3, 140.9, 137.5, 134.7, 123.5, 123.0, 120.9, 117.6, 110.9, 71.9, 67.3, 56.7, 56.0, 45.8, 45.7, 44.6, 40.6, 39.7, 31.0, 29.7, 28.7, 27.1, 25.7, 25.6, 23.2, 21.8, 21.3, 18.0, 17.9, 16.9, 12.0, -4.9, -5.0, -5.3 ppm.

Preparation 108: Compound 528

510 (0.15 g)
9-acetyl-anthracene (0.02 g)
DCM

528: δ_H in agreement with structure.

Preparation 109: Compound 529

511 (24 mg, 0.04 mmol)
9-acetyl-anthracene
toluene

529: δ_H in agreement with structure.

Preparation 110: Compound 530

514 (125 mg, 0.2 mmol)
9-acetyl-anthracene
DCM

530: δ_H in agreement with structure.

Preparation 111: Compound 531

515 (17 mg)
anthracene (0.01 g)
toluene (2 ml)

531: δ_H in agreement with structure.

Preparation 112: Compound 532

516 (90 mg)
9-acetyl-anthracene
DCM

532: δ_H in agreement with structure.

Preparation 113: Compound 533

517 (0.10 g, 0.16 mmol)
9-acetyl-anthracene
DCM

533: δ_H 6.23 (d, 1H), 6.03 (d,1H, J=15.6 Hz), 6.01 (d, 1H), 5.88 (dd, 1H, J=8.4 Hz and 15.6 Hz), 5.17 (m, 1H), 4.86 (m, 1H), 4.78 (m, 1H), 4.72 (m, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 2.83 (m, 1H), 2.45 (dd,1H), 2.30 - 2.06 (m, 2H), 2.05 - 1.95 (m, 2H), 1.07 (d, 3H), 0.87 (s, 18H), 1.93 - 0.80 (m, 12H), 0.67 (m, 2H), 0.56 (s, 3H), 0.41 (m, 2H), 0.05 (m, 6H), 0.04 (m, 6H) ppm.

Preparation 114: Compound 520

518 (57 mg)
anthracene (0.05 g)
DCM

Chromatography: 0.5% ether in petroleum ether

520: δ_H 6.87 (d, J=9.9Hz, 1H), 6.22 (d, J=11.2Hz, 1H), 6.00 (d, J=11.2Hz, 1H), 6.01 (dd, J=9.9Hz, J=15.3Hz, 1H), 5.81 (dd, J=15.3Hz, J=9.5Hz, 1H), 5.17 (bm, 1H), 4.85 (bm, 1H), 4.36 (m, 1H), 4.19 (m, 1H), 2.81 (bm, 1H), 2.44 (dd, 1H), 2.2 - 1.0 (m, 15H), 0.95 (d, J=6.6Hz, 3H), 0.87 (bs, 18H), 0.50 (s, 3H), 0.05 (bs, 12H) ppm.

Preparation 115: Compound 1002

1001 (104 mg, 0.17 mmol)
9-acetylanthracene
tert-butyl methyl ether

1002: δ_H in agreement with structure.

Preparation 116: Compound 1004

1003 (41 mg)

9-acetylanthracene (10 mg)

toluene (4 ml)

1004: δ_H 6.23 (d, 1H), 6.00 (d,1H), 5.17 (m, 1H), 4.85 (m, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 2.82 (m, 1H), 2.44 (dd,1H), 1.52 (s, 6H), 1.17 (d, 3H), 0.87 (s, 18H), 2.38 - 0.80 (m, 16H), 0.56 (s, 3H), 0.05 (s, 6H), 0.04 (s, 6H) ppm.

Preparation 117: Compound 1006

1005 (70 mg, 0.1 mmol)

anthracene (80 mg)

DCM

1006: δ_C 148.1, 140.0, 135.2, 122.8, 118.0, 111.0, 85.1, 78.4, 72.5, 71.7, 69.3, 67.3, 64.8, 55.7, 55.5, 45.8, 45.5, 44.6, 39.5, 34.1, 28.6, 28.3, 26.4, 25.6, 25.6, 23.0, 21.9, 20.7, 18.0, 17.9, 12.2, 8.3, -4.9, -5.0, -5.3 ppm.

Preparation 118: Compound 1008

1007 (68 mg, 0.1 mmol)

9-acetylanthracene

DCM

1008: δ_H 6.23 (d, 1H), 6.00 (d,1H), 5.17 (m, 1H), 4.85 (m, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 2.83 (m, 1H), 2.44 (dd,1H), 1.17 (d, 3H), 1.03 (t, 6H), 0.87 (s, 18H), 2.38 - 0.80 (m, 20H), 0.56 (s, 3H), 0.05 (m, 6H), 0.04 (m, 6H) ppm.

General Procedure 8 (Examples 4, 14-18)

To a mixture, maintained at about 25 °C, of an ethyl acetate solution (about 0.3 ml) of the appropriate

silyl-protected compound (ca. 0.1 mmol)

in acetonitrile (4 ml) was added (via plastic pipette) 40% aqueous hydrofluoric acid (0.5 ml, ca. 10 mmol). After vigorous stirring at the same temperature for 1 h, the reaction mixture was partitioned between ethyl acetate and 3N sodium hydroxide (to alkaline reaction to pH paper) solution before standard work-up to give the compound I.

General Procedure 9 (Examples 1-3, 5-13)

To a solution of the appropriate

silyl-protected compound (0.1 mmol)

in THF (4 ml) was added solid TBA-fluoride trihydrate (0.13g, ca. 0.4 mmol), and the solution was heated at 60°C for one hour. After cooling (and partial concentration in vacuo when the volume of THF in a scaled-up procedure exceeded 30 ml), 0.2 M aqueous sodium hydrogen carbonate solution and ethyl acetate were added. Standard work-up gave the compound I.

Example 1: 1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 1)

A solution of 519 (2.1 g, 3.36 mmol) and tetra-n-butylammonium fluoride trihydrate (5.42 g, 17.2 mmol) in tetrahydrofuran (70 ml) was heated at 60°C in an argon atmosphere for 60 minutes. After cooling and concentration *in vacuo*, the reaction mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was washed with water and brine, dried and concentrated. The residue was purified by chromatography (50% ethyl acetate in petroleum ether). Fractions containing the title compound were concentrated *in vacuo* to yield an oil which gave colourless crystals from methyl formate. 1: δ_C 147.7, 143.1, 138.2, 132.9, 132.8, 125.3, 125.0, 124.3, 117.1, 111.8, 70.8, 66.9, 56.4, 45.9, 45.3, 42.9, 40.5, 40.4, 29.1, 27.8, 25.9, 23.6, 22.3, 20.8, 18.2, 12.3 ppm.

Example 2: 1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(Z),24-penta-ene (Compound 2)

521 (32 mg, 0.05 mmol)

2: δ_H in accordance with structure.

Example 3: 1(S),3(R)-Dihydroxy-9,10-seco-20(S)-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 3)

523 (135 mg, 0.22 mmol)

Chromatography: 40% ethyl acetate in petroleum ether

3: δ_C 147.7, 143.4, 138.6, 132.8, 132.5, 125.3, 125.0, 124.3, 116.9, 111.8, 70.9, 66.9, 56.9, 56.2, 46.0, 45.3, 42.9, 40.9, 39.7, 29.1, 27.3, 25.9, 23.5, 22.1, 21.5, 18.3, 12.2 ppm.

Example 4: 1(S),3(R)-Dihydroxy-9,10-seco-26,27-cyclo-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 4)

524 (36 mg)

Chromatography: 50% ethyl acetate in petroleum ether

4: δ_H 6.37 (d, J=11Hz, 1H), 6.34 (bd, J=10Hz, 1H), 6.11 (dd, J=10Hz, J=15Hz, 1H), 6.01 (d, J=11Hz, 1H), 5.56 (dd, J=9Hz, J=15Hz, 1H), 5.32 (bs, 1H), 5.00 (bs, 1H), 4.43 (m,

1H), 4.23 (m, 1H), 2.83 (dd, J=4Hz, J=11Hz, 1H), 2.59 (dd, J=4Hz, J=13Hz, 1H), 2.31 (dd, J=6Hz, J=13Hz, 1H), 2.2 - 1.2 (m, 16H), 1.10 (m, 4H), 1.07 (d, J=7Hz, 3H), 0.58 (s, 3H) ppm.

Example 5: 1(S),3(R)-Dihydroxy-9,10-seco-26,27-cyclo-20(S)-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 5)

525 (165 mg, 0.26 mmol)

Chromatography: 50% ethyl acetate in petroleum ether

5: δ_C 147.7, 143.2, 139.5, 132.9, 127.1, 125.0, 123.9, 119.1, 117.0, 111.8, 70.8, 66.8, 56.9, 56.2, 46.0, 45.3, 42.9, 40.7, 39.8, 29.1, 27.3, 23.5, 22.1, 21.3, 12.3, 2.4, 2.2 ppm.

Example 6: 1(S),3(R)-Dihydroxy-9,10-seco-26,27-methano-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 6)

526 (348 mg, 0.55 mmol)

Isolation from the crude product by direct crystallisation from methyl formate, omitting the chromatography step

6: δ_C 147.6, 143.1, 142.8, 137.2, 133.0, 125.0, 123.9, 121.0, 117.1, 111.8, 70.8, 66.9, 56.4, 56.4, 45.9, 45.3, 42.9, 40.4, 40.4, 31.3, 29.9, 29.1, 27.8, 23.6, 22.2, 20.8, 17.2, 12.3 ppm.

Example 7: 1(S),3(R)-Dihydroxy-9,10-seco-26,27-methano-20(S)-cholesta-5(Z),7(E),10(19),22(E),24-penta-ene (Compound 7)

527 (150 mg, 0.23 mmol)

Chromatography: 40% ethyl acetate in petroleum ether

7: δ_C 147.7, 143.3, 142.6, 137.6, 132.8, 125.0, 123.8, 121.1, 116.9, 111.8, 70.9, 66.9, 56.9, 56.2, 46.0, 45.3, 42.9, 40.8, 39.8, 31.3, 29.9, 29.1, 27.3, 23.5, 22.1, 21.5, 17.1, 12.2 ppm.

Example 8: 1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 9)

528 (148 mg, 0.23 mmol)

recrystallised from methyl formate

9: δ_H (in hexadeuterioacetone) 6.29 (d, 1H), 6.25 (dd, 1H, J=11.1 Hz and 15.1 Hz), 6.09 (d, 1H), 5.99 (d, 1H, J=11.1 Hz), 5.52 (dd, 1H, J=8.8 Hz and 15.1 Hz), 5.31 (m, 1H), 4.86 (m, 1H), 4.39 (m, 1H), 4.17 (m, 1H), 3.96 (d, 2H), 3.86 (d, OH), 3.68 (t, OH), 3.62 (d, OH), 2.87 (m, 1H), 2.50 (dd, 1H), 2.29 (dd, 1H), 2.20 (m, 1H), 1.72 (bs, 3H), 2.10 - 1.20 (m, 13H), 1.08 (d, 3H), 0.60 (s, 3H) ppm.

Example 9: 1(S),3(R),26-Trihydroxy-9,10-seco-20(S)-cholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 10)

529 (0.126 g, 0.2 mmol)

10: δ_C 147.7, 143.2, 141.8, 134.5, 132.9, 125.5, 125.0, 123.4, 117.0, 111.8, 70.9, 68.7, 66.8, 56.8, 56.2, 46.0, 45.3, 42.9, 41.0, 39.8, 29.1, 27.2, 23.5, 22.1, 21.3, 14.2, 12.3 ppm.

Example 10: 1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(Z)-penta-ene (Compound 11)

530 (24 mg, 0.04 mmol)

11: δ_H 6.38 (d, 1H), 6.22 (dd, 1H, J=11.1 Hz and 14.9 Hz), 6.01 (d, 1H), 5.88 (d, 1H, J=11.1 Hz), 5.51 (dd, 1H, J=8.8 Hz and 14.9 Hz), 5.32 (m, 1H), 5.00 (m, 1H), 4.43 (m, 1H), 4.24 (s, 2H), 4.22 (m, 1H), 2.83 (m, 1H), 2.60 (dd, 1H), 2.31 (dd, 1H), 2.13 (m, 1H), 1.85 (bs, 3H), 1.05 (d, 3H), 2.08 - 0.80 (m, 16H), 0.56 (s, 3H) ppm.

Example 11: 1(S),3(R),26-Trihydroxy-9,10-seco-20(S)-cholesta-5(Z),7(E),10(19), 22(E),24(Z)-penta-ene (Compound 12)

531 (17 mg, 0.03 mmol)

12: δ_H 6.37 (d, 1H), 6.20 (dd, 1H, J=11.1 Hz and 14.9 Hz), 6.01 (d, 1H), 5.89 (d, 1H, J=11.1 Hz), 5.52 (dd, 1H, J=9.5 Hz and 14.9 Hz), 5.33 (m, 1H), 5.00 (m, 1H), 4.43 (m, 1H), 4.24 (s, 2H), 4.22 (m, 1H), 2.81 (m, 1H), 2.60 (dd, 1H), 2.31 (dd, 1H), 1.86 (bs, 3H), 0.94 (d, 3H), 2.20 - 0.80 (m, 17H), 0.50 (s, 3H) ppm.

Example 12: 1(S),3(R)-Dihydroxy-20(R)-(4-methyl-5-ethyl-5-hydroxy-1(E),3(E)-heptadienyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 13)

532 (90 mg, 0.13 mmol)

13: δ_C 147.7, 143.0, 140.2, 137.5, 133.0, 125.0, 124.6, 124.0, 117.1, 111.8, 78.4, 70.8, 66.8, 56.4, 56.4, 46.0, 45.3, 42.9, 40.5, 40.4, 31.8, 29.1, 27.7, 23.6, 22.3, 20.6, 14.2, 13.5, 12.3, 7.7 ppm.

Example 13: 1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-1(E),3-butadienyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 14)

533 (0.10 mg, 0.16 mmol)

recrystallised from methyl formate

14: δ_C 147.8, 147.7, 143.1, 137.0, 133.0, 129.9, 125.0, 117.1, 111.8, 110.5, 70.8, 66.9, 56.5, 56.4, 46.0, 45.3, 42.9, 40.4, 40.3, 29.1, 27.6, 23.6, 22.2, 20.6, 12.8, 12.3, 5.5 ppm.

Example 14: 1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),24-tetra-ene-22-yne (Compound 15)

1002 (100 mg, 0.16 mmol)

Chromatography: 50% ethyl acetate in petroleum ether

15: δ_C 147.4, 146.1, 142.6, 132.9, 124.7, 117.0, 111.6, 105.4, 96.4, 78.9, 70.6, 66.6, 56.1, 55.8, 45.6, 45.1, 42.7, 39.5, 28.8, 28.3, 26.3, 24.4, 23.2, 22.1, 21.6, 20.5, 12.3 ppm.

Example 15: 1(S),3(R)-Dihydroxy-20(R)-(5-methyl-5-hydroxy-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 16)

1004 (41 mg, 0.06 mmol)

16: δ_C 147.7, 142.7, 133.2, 124.9, 117.1, 111.8, 85.8, 80.6, 70.8, 67.4, 66.8, 65.6, 65.4, 55.9, 55.6, 45.9, 45.2, 42.9, 39.3, 31.2, 29.1, 28.2, 27.3, 23.5, 21.9, 20.5, 12.4 ppm.

Example 16: 1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1,3-heptadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 17)

1006 (66 mg, 0.1 mmol)

17: δ_C 147.6, 142.4, 133.4, 124.8, 117.4, 111.9, 85.1, 78.8, 72.7, 70.9, 69.4, 66.9, 65.3, 55.9, 55.8, 45.9, 45.3, 42.9, 39.6, 34.3, 29.0, 28.4, 26.3, 23.3, 22.2, 21.0, 12.5, 8.5 ppm.

Example 17: 1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1,3-heptadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 18)

1008 (69 mg, 0.1 mmol)

18: δ_C 147.7, 142.7, 133.2, 124.9, 117.1, 111.8, 85.2, 79.0, 72.7, 70.8, 69.4, 66.9, 65.6, 55.9, 55.6, 45.9, 45.3, 42.9, 39.3, 34.3, 29.1, 28.2, 27.3, 23.5, 22.0, 20.4, 12.4, 8.5 ppm.

Example 18: 1(S),3(R)-Dihydroxy-20(S)-(4,4-dibromo-1,3-butadien-1yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene (Compound 8)

520 (75 mg, 0.1 mmol)

Chromatography: 50% ether in petroleum ether

8: δ_C 147.4, 145.7, 142.6, 137.0, 132.9, 124.7, 124.7, 116.9, 111.6, 88.1, 70.6, 66.6, 56.4, 55.9, 45.7, 45.0, 42.7, 40.7, 39.5, 28.8, 26.9, 23.2, 21.8, 20.5, 12.1 ppm.

Example 19: 1(S)-Fluoro-3(R)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 21)

Example 20: 1(S),3(R)-Dihydroxy-19-nor-9,10-secocholesta-5,7(E),22(E),24-tetra-ene (Compound 22)

Example 21: 1(S),3(S)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),22(E),24-penta-ene (Compound 23)

Example 22: 1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),16,22(E),24-hexa-ene (Compound 24)

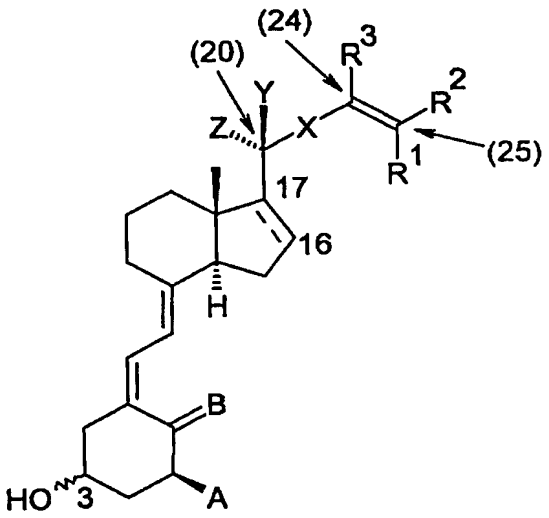
Example 23: 1(S),3(R)-Dihydroxy-26,26,26,27,27,27-hexafluoro-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 25)

Example 24: Capsules containing Compound 1

Compound 1 was dissolved in arachis oil to a final concentration of 10 μg of Compound 1/ml oil. 10 Parts by weight of gelatine, 5 parts by weight glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by weight distilled water were mixed together with heating and formed into soft gelatine capsules. These were then filled each with 100 μl of Compound 1 in oil solution, such that each capsule contained 1 μg of Compound 1.

CLAIMS

1. A compound according to formula I



I

in which formula

R1 and R2, which may be the same or different, represent hydrogen, halogen, (C_1-C_6)hydrocarbyl optionally substituted with one or two hydroxyl group or one or more fluorine atoms, or, together with the carbon atom to which they are both attached, R1 and R2 form a (C_3-C_6)carbocyclic ring, or one of R1 and R2 taken together with R3 forms a direct bond, such that a triple bond is constituted;

R3 when not forming a direct bond with one of R1 and R2 represents hydrogen or (C_1-C_3)hydrocarbyl;

X represents ethynylene or, when R3 is hydrogen or hydrocarbyl, ethylene or ethynylene;

Y and Z independently represent hydrogen or methyl;

the bond between C#16 and C#17 is depicted with a dotted line to illustrate that said bond may be either a single bond, in which case the projection of the ring substituent is beta, or a double bond;

A represents hydroxyl, fluorine or hydrogen;

B represents CH_2 or H_2;

with the proviso that the compound of formula I is not 3(S)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene;

and prodrugs thereof.

2. A compound according to claim 1 wherein R1 and R2 when taken separately represent methyl, trifluoromethyl, hydroxymethyl, (1- or 2-)hydroxyethyl, normal, iso- or cyclopropyl, 2-hydroxy-2-propyl, 2-methyl-2-propyl, 3-pentyl or 3-hydroxy-3-pentyl.

3. A compound according to claim 1 or 2 wherein A is hydroxyl or fluoro.

4. A compound according to claim 1 wherein R2 constitutes part of a triple bond and R1 represents a branched C_{1-6}hydrocarbyl, optionally substituted by one or two hydroxyl groups.

5. A compound according to claim 4 wherein R1 represents- CMe_3, $-C(OH)Me_2$ or $-C(OH)Et_2$.

6. A compound according to claim 1 wherein R3 represents hydrogen, methyl or cyclopropyl.

7. A compound according to claim 1 wherein R1 and R2 when taken together with the carbon atom to which they are both attached form a (C_3-C_6)carbocyclic ring

8. A compound according to claim 7 wherein R1 and R2 when taken together are ethylene, tri-, tetra- and penta-methylene.

9. A compound according to claim 1 selected from the list consisting of
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 1),
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(Z),24-penta-ene (Compound 2),
20(S),1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 3),
1(S),3(R)-Dihydroxy-9,10-seco-26,27-cyclo-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 4),
20(S),1(S),3(R)-Dihydroxy-9,10-seco-26,27-cyclo-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 5),
1(S),3(R)-Dihydroxy-9,10-seco-26,27-methano-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 6),
20(S),1(S),3(R)-Dihydroxy-9,10-seco-26,27-methano-cholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 7),

1(S),3(R)-Dihydroxy-20(S)-(4,4-dibromo-1,3-butadien-1yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene (Compound 8),
1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 9),
20(S),1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 10),
1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(Z)-penta-ene (Compound 11),
20(S),1(S),3(R),26-Trihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(Z)-penta-ene (Compound 12),
1(S),3(R)-Dihydroxy-20(R)-(4-methyl-5-ethyl-5-hydroxy-1(E),3(E)-heptadienyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 13),
1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-1(E),3-butadienyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 14),
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),24-tetra-ene-22-yne (Compound 15),
1(S),3(R)-Dihydroxy-20(R)-(5-methyl-5-hydroxy-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 16),
1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1,3-heptadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 17),
1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1,3-heptadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 18),
1(S),3(R)-Dihydroxy-20(R)-(5,5-dimethyl-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 19),
1(S),3(R)-Dihydroxy-20(S)-(5,5-dimethyl-1,3-hexadiynyl)-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 20),
1(S)-Fluoro-3(R)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 21),
1(S),3(R)-Dihydroxy-19-nor-9,10-secocholesta-5,7(E),22(E),24-tetra-ene (Compound 22),
1(S),3(S)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),22(E),24-penta-ene (Compound 23),
1(S),3(R)-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19),16,22(E),24-hexa-ene (Compound 24),
1(S),3(R)-Dihydroxxy-26,26,26,27,27,27-hexafluoro-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene (Compound 25),
3(S),26-Dihydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24(E)-penta-ene (Compound 26).

10. A compound according to any of claims 1-9 for use in therapy.

11. A pharmaceutical composition comprising a compound according to any of claims 1-9, optionally another therapeutically active compound, and optionally a pharmaceutically acceptable carrier.

12. A composition according to claim 11, wherein said other therapeutically active compound is selected from amongst phosphate binders, steroids and anti-proliferative agents.

13. A composition according to claims 11 or 12 in unit dosage form.

14. A method for treatment or prophylaxis of diseases characterised by abnormal cell differentiation and/or cell proliferation, cancer, leukemia, mammary cancer, brain glial cancer, osteosarcoma, melanoma, myelofibrosis, psoriasis, primary hyperparathyroidism, diabetes melitus, discoid and systemic lupus erythematosus, chronic dermatoses of autoimmune type, hypertension, acne, alopecia, skin aging, AIDS, neurodegenerative disorders, Alzheimer's disease, host versus graft and graft versus host reactions, rejections of transplants, steroid induced skin atrophy and osteroporosis, and inducing osteogenisis,, the method comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1-9, optionally together with another therapeutically active compound.

15. A method for treatment of prophylaxis of secondary hyperparathyroidism, the method comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1-9, optionally together with another therapeutically active compound.

16. A method according to claim 15, wherein secondary hyperparathyroidism is associated with renal failure.

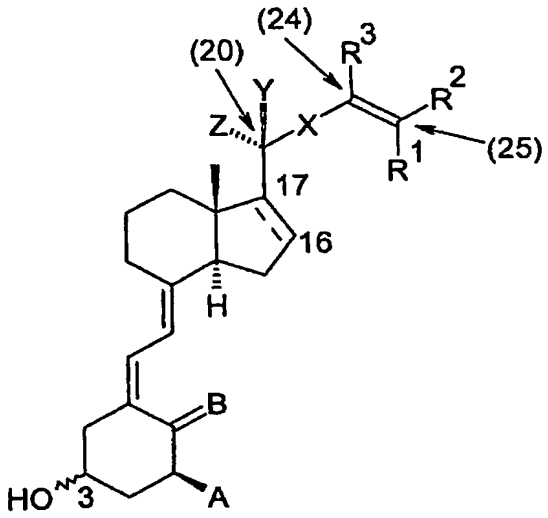
17. A method according to any of claims 14-16, wherein said other therapeutically active compound is selected from amongst phosphate binders, steroids and anti-proliferative agents.

18. The use of a compound according to any of claims 1-9, optionally together with another therapeutically active compound, in the manufacture of a medicament for the treatment or amelioration of diseases selected from the list consisting of diseases characterised by abnormal cell differentiation and/or cell proliferation, cancer, leukemia, mammary cancer, brain glial cancer, osteosarcoma, melanoma, myelofibrosis, psoriasis, primary hyperparathyroidism, secondary hyperparathyroidism, secondary parathyroidism associated with renal faiure, diabetes melitus, discoid and systemic lupus erythematosus, chronic dermatoses of autoimmune type, hypertension, acne, alopecia, skin aging, AIDS, neurodegenerative disorders, Alzheimer's disease, host versus graft and graft versus host reactions, rejections of transplants, steroid induced skin atrophy and osteroporosis, and for inducing osteogenisis,.

19. The use according to claim 18, wherein said other therapeutically active compound is selected from amongst phosphate binders, steroids and anti-proliferative agents.

ABSTRACT

Compounds according to formula I



I

in which formula R1 and R2, which may be the same or different, represent hydrogen, halogen, (C_1-C_6)hydrocarbyl optionally substituted with one or two hydroxyl group or one or more fluorine atoms, or, together with the carbon atom to which they are both attached, R1 and R2 form a (C_3-C_6)carbocyclic ring, or one of R1 and R2 taken together with R3 forms a direct bond, such that a triple bond is constituted; R3 when not forming a direct bond with one of R1 and R2 represents hydrogen or (C_1-C_3)hydrocarbyl; X represents ethynylene or, when R3 is hydrogen or hydrocarbyl, ethylene or ethynylene; Y and Z independently represent hydrogen or methyl; the bond between C#16 and C#17 is depicted with a dotted line to illustrate that said bond may be either a single bond, in which case the projection of the ring substituent is beta, or a double bond; A represents hydroxyl, fluorine or hydrogen; B represents CH_2 or H_2; with the proviso that the compound of formula I is not 3(S)-hydroxy-9,10-secocholesta-5(Z),7(E),10(19), 22(E),24-penta-ene;
and prodrugs thereof are provided together with their use in therapy, and their use in the manufacture of medicaments.